63. (New) The *lin-37* nucleic acid of claim 62, wherein said *lin-37* nucleic acid has the ability to decrease cell proliferation by 50%.

64. (New) The *lin-37* nucleic acid of claim 62, wherein said *lin-37* nucleic acid has the ability to decrease cell proliferation by one fold.

REMARKS

The Office Action

Claims 1, 4-7, 10-18, and 25 are pending. Claims 1, 4-7, 10-18 and 25 were rejected under 35 U.S.C. § 101, and under 35 U.S.C. § 112, first paragraph, for not being supported by a specific and substantial utility, thereby failing to enable the claimed invention. In addition, claims 1, 5, 15, and 25 were rejected under 35 U.S.C. § 102(a) as being anticipated by Lu and Horvitz (East Coast *C. elegans* Meeting, June 9-11, 1996); claims 1, 3, and 5 were rejected under 35 U.S.C. § 102(a) as being anticipated by Ceol and Horvitz (East Coast *C. elegans* Meeting, June 9-11, 1996); claims 1, 3, 5, 11, and 14-16 were rejected under 35 U.S.C. § 102(a) as being anticipated by Lu and Horvitz (11th International *C. elegans* Meeting, May 28-June 1, 1997); and claim 25 was rejected under 35 U.S.C. § 102(a) as being anticipated by Ceol and Horvitz (11th International *C. elegans* Meeting, May 28-June 1, 1997). Each of these rejections is addressed as follows.

Support for the New Claims

Applicants now add new claims 34-64. New claims 34, 40, 46, 52, 58, and 61 are based on original claims 1, 10, 16, 18, and 25, and are drawn to naturally-occurring synMuv nucleic

acid sequences, support for which may be found, for example, on page page 18, line 23, to page 19, line 2, page 19, lines 7-15, and page 36, line 9, to page 37, line 15, of the specification. In addition, new claims 35, 47, and 53 refer to nucleic acids that encode a LIN-37 polypeptide that has 85% or greater amino acid sequence identity to the amino acid sequence of SEQ ID NO:1, and claims 41 and 59 refer to a synMuv nucleic acid having a nucleic acid sequence that has 85% or greater nucleotide sequence identity to the nucleotide sequence of SEQ ID NO:2, support for which may be found on page 10, lines 20-23. Similarly, new claims 36, 48, and 54 refer to nucleic acids that encode a LIN-37 polypeptide that has 95% or greater amino acid sequence identity to the amino acid sequence of SEQ ID NO:1, and claims 42 and 60 refer to synMuv nucleic acids having a nucleic acid sequence that has 95% or greater nucleotide sequence identity to the nucleotide sequence of SEQ ID NO:2, support for which may be found on page 10, lines 20-23. Furthermore, new claims 37-39, 43-45, 49-51, 55-57, and 62-64, which refer to nucleic acids encoding synMuv or LIN-37 polypeptides that have the ability to decrease cell proliferation, find support in the specification, for example, on page 10, lines 15-18.

Rejections under 35 U.S.C. § 101

Claims 1, 4-7, 10-18, and 25 were rejected under 35 U.S.C. § 101 on the basis that the claimed invention is not supported by a specific, asserted, credible, or well-established utility.

The Examiner states:

> There are no teachings in the specification to provide any objective evidence that the synMuv polypeptides can modulate cell proliferation in human cells or any mammalian cells, nor is there any objective evidence that these peptides could be used as potential anti-neoplastic or anti-tumor agents.

Applicants respectfully disagree with these assertions and draw the Examiner's attention to their specification, where, on page 2, lines 5-12, Applicants note that the genes that, when mutated, lead to the Muv phenotype in *C. elegans*, are part of a Ras signal transduction pathway. Ras pathways have been found to control cell proliferation in a range of organisms and mutations in members of this pathway have been found in a broad range of human cancers. As is stated by Hunter (*Cell* 88:333-346, 1997; copy enclosed) on page 337, in the second paragraph, the frequency of Ras mutations is among the highest for any gene in human cancers. Accordingly, synMuv nucleic acid and amino acid sequences, which act as negative regulators of this conserved signal transduction pathway, can reasonably be expected to serve as therapeutic agents for a variety of cell proliferative diseases. The claimed nucleic acids therefore have the substantial utility of providing a likely therapy for a disease for which a treatment would be desirable.

In particular, as is noted in the specification on page 3, lines 7-13, various synMuv genes encode proteins that are part of signaling pathway that is analogous to the Rb signaling pathway in mammals. Moreover, as is stated in the specification on page 17, lines 15-17:

> Most commonly, inactivation of Rb results in a rare eye cancer, retinoblastoma, although inactivating mutations in Rb have been found in other types of tumors.

Consequently, Rb, the mammalian homologue of the *C. elegans* synMuv pathway protein LIN-35, can modulate cell proliferation in mammalian cells. Furthermore, other members of the synMuv pathway are proteins whose mammalian homologues either bind, such as p48 (the mammalian homologue of LIN-53), or are likely to bind, such as a complex of DP (the mammalian homologue of LIN-55) and E2F (the mammalian homologue of E2F-1), to Rb. In light of these observations, one also would expect *lin-37* nucleic acids that encode a synMuv

protein to modulate cell proliferation in a mammal as they do in *C. elegans* and, therefore, to be useful as anti-neoplastic or anti-tumor agents.

In addition, Applicants' specification, for example, on page 16, line 22, to page 17, line 2, and page 18, line 18, to page 19, line 2, describes further specific uses for the claimed *lin-37* synMuv nucleic acids, including their use in the identification of additional tumor suppressors in mammals and in increasing our understanding of cell proliferative diseases.

In view of the above arguments, Applicants submit that the claimed nucleic acids have a substantial, as well as a specific utility. Accordingly, the rejection of claims 1, 4-7, 10-18, and 25 under 35 U.S.C. § 101 should be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1, 4-7, 10-18, and 25 were rejected under 35 U.S.C. § 112, first paragraph, on the basis that the claimed invention is not supported by a well established utility and that the specification does not reasonably provide enablement commensurate with the scope of the claimed invention. The 35 U.S.C. § 112, first paragraph rejection of claims 1, 4-7, 10-18, and 25 for lacking a well established utility is addressed with the arguments presented in response to the 35 U.S.C. § 101 rejection in the above section. For the following reasons, Applicants submit that the 35 U.S.C. § 112, first paragraph rejection of claims 1, 4-7, 10-18, and 25 for failing to enable the claimed invention is respectfully traversed.

The Examiner states:

> ...the specification has not taught that it is possible to alter the amino acid sequence of SEQ ID NO:1 and retain the same claimed activity of the synMuv polypeptide, nor has the specification given any guidance on which amino acids in the synMuv polypeptide will tolerate substitutions.

The present application clearly sets forth a method for identifying synMuv nucleic acid and amino acid sequences besides the ones provided in SEQ ID NOS:1 and 2. Prior case law establishes that the specification need not explicitly teach every possible embodiment of the invention. As stated in *Scripps Clinic & Research Foundation v. Genentech, Inc.*, "the purpose of [the enablement] provision is to assure that the inventor provides sufficient information about the claimed invention that a person of skill in the field of the invention can make and use it without undue experimentation, relying on the patent specification and the knowledge in the art," See, 18 USPQ2d 1896, 1006 (Fed. Cir. 1991). Similarly, *In re Vaeck* states that "[t]he first paragraph of 35 U.S.C. § 112 requires, *inter alia*, that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without 'undue experimentation'... That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is 'undue,'" See, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). Based on the following arguments, Applicants submit that the presently claimed nucleic acid sequences may be identified without undue experimentation.

The specification not only describes the identification and isolation of *lin-37*, but also of a number of other synMuv nucleic acid sequences, including *lin-35, lin-52, lin-53, lin-54, lin-55*, and *C. elegans* E2F-1. Moreover, the specification provides a method for identifying further synMuv nucleic acid sequences that have the ability to alter cell proliferation. In support of this statement, Applicants draw the Examiner's attention to Example XII, (page 28, line 10 to page 29, line 24, of the specification). Here, Applicants provide several screening methods for

molecules that either increase or decrease synMuv expression in a cell. One approach involves adding a candidate molecule to a culture medium of cells or nematodes expressing a synMuv mRNA and assaying synMuv mRNA expression in the presence of the candidate molecule, in comparison to synMuv mRNA expression in the absence of the candidate molecule. These expression assays may be performed using standard techniques such as Northern analysis. Moreover, one skilled in the art, using the methods described in this example, could readily quantify the expression of a protein encoded by a synMuv nucleic acid in such cells or nematodes. These screening methods also can easily be adapted to high-throughput protocols, enabling a skilled artisan to screen candidate molecules rapidly and without undue experimentation. Furthermore, once identified, a polypeptide encoded by a synMuv nucleic acid can be isolated using the techniques described in Applicants' specification, for example, on page 25, line 22, to page 26, line 1. Accordingly, the teachings of the specification provide methods for identifying synMuv molecules that have the claimed function, namely the ability to alter cell proliferation, and one skilled in the art would therefore be able to use these methods to identify such synMuv molecules. In view of these arguments, Applicants submit that the presently claimed synMuv nucleic acid sequences are enabled and that the 35 U.S.C. § 112, first paragraph, rejection of claims 1, 4-7, 10-18, and 25 should be withdrawn.

In addition, new claims 35, 36, 41, 42, 47, 48, 53, 54, 59, and 60, which refer to synMuv nucleic acids that are at least 85% or 95% identical to SEQ ID NO:2, or to synMuv nucleic acids encoding polypeptides that are at least 85% or 95% identical to SEQ ID NO:1, are also clearly enabled in light of the above arguments.

Applicants add new claims 34, 40, 46, 52, 58, and 61 which are drawn to naturally-occurring synMuv nucleic acid sequences. As is stated in Applicants' specification on page 2,

lines 9-12, the Ras signal transduction pathway has been found to control cell proliferation and exists in a range of different organisms. Moreover, the nucleic acids encoding the proteins that make up this signaling pathway occur naturally in these organisms. Accordingly, the claimed, naturally-occurring synMuv nucleic acid sequences which act as negative regulators of the conserved Ras signal transduction pathway also are likely to be capable of altering cell proliferation. Furthermore, one skilled in the art of molecular biology would know how to isolate a naturally-occurring nucleic acid sequence from an organism using standard methods. Consequently, Applicants submit that the naturally-occurring synMuv nucleic acids are enabled by their specification.

Applicants also add new claims 37-39, 43-45, 49-51, 55-57, and 62-64 which refer to synMuv (e.g., *lin-37*) nucleic acids that have the ability to decrease cell proliferation. As is stated above, the application provides screening methods for identifying additional synMuv molecules. For example, the cell lineage of each cell in *C. elegans* is known and numerous phenotypes associated with abnormal cell proliferation can be identified as described in, for example, Horvitz and Sulston (*Genetics* 96:435-454, 1980; copy enclosed). Accordingly, one skilled in the art, using standard methods, would be able to determine if the addition of a molecule to such an assay results in a decrease in cell proliferation, in particular a decrease of 50% or one-fold. Furthermore, Applicants' specification, for example, on page 28, line 10, to page 29, line 24, provides methods that may be used by one skilled in the art to observe a decrease in cell proliferation in response to the addition of a candidate molecule. Consequently, Applicants submit that new claims 37-39, 43-45, 49-51, 55-57, and 62-64 are enabled by their specification.

Rejections under 35 U.S.C. § 102(a)

Claims 1, 5, 15, and 25 were rejected under 35 U.S.C. § 102(a) as being anticipated by Lu and Horvitz (East Coast *C. elegans* Meeting, June 9-11, 1996); claims 1, 3, and 5 were rejected under 35 U.S.C. § 102(a) as being anticipated by Ceol and Horvitz (East Coast *C. elegans* Meeting, June 9-11, 1996); claims 1, 3, 5, 11, and 14-16 were rejected under 35 U.S.C. § 102(a) as being anticipated by Lu and Horvitz (11th International *C. elegans* Meeting, May 28-June 1, 1997); and claim 25 was rejected under 35 U.S.C. § 102(a) as being anticipated by Ceol and Horvitz (11th International *C. elegans* Meeting, May 28-June 1, 1997). This rejection may be withdrawn for the following reasons.

Neither the Ceol and Horvitz (East Coast *C. elegans* Meeting, June 9-11, 1996), nor the Ceol and Horvitz (11th International *C. elegans* Meeting, May 28-June 1, 1997) abstract describes the invention as claimed. The Ceol and Horvitz (1996) abstract refers to methods that may be used to isolate synMuv genes. However, this abstract fails to provide a *lin-37* nucleic acid sequence, much less one that has 50% or greater identity to SEQ ID NO:2 or one that encodes an amino acid sequence having 50% or greater identity to SEQ ID NO:1. The Ceol and Horvitz (1997) abstract describes the cloning of *lin-52* and *lin-55*; it is silent on *lin-37*. Accordingly, this abstract clearly fails to describe the presently claimed *lin-37* nucleic acid sequences. In addition, since these abstracts lack a description of a *lin-37* nucleic acid sequence, isolating *lin-37* nucleic acids also would not have been obvious to one skilled in the art in view of these references.

Turning to the Lu and Horvitz (East Coast *C. elegans* Meeting, June 9-11, 1996) and Lu and Horvitz (11th International *C. elegans* Meeting, May 28-June 1, 1997) abstracts, Applicants submit that these references are not prior art under 35 U.S.C. § 102(a). As is stated under 102(a),

if Applicant's disclosure of his or her own work is within the year before the application filing date, it cannot be used against him or her under 35 U.S.C. § 102(a) (see M.P.E.P. 2132.01 and *In re Katz* 687 F.2d 450, 215 USPQ 14 (CCPA 1982). In this regard, Applicants draw the Examiner's attention to the Request to Correct Inventorship under 37 C.F.R. § 1.48(b), submitted herewith, where Applicants state that the prosecution of this application has resulted in the cancellation of claims to the inventions made by Craig Ceol. As a result of this correction, the inventors of the presently claimed invention are Xiaowei Lu and H. Robert Horvitz, the authors of above-cited abstracts. Since these abstracts were published less than one year before the May 28, 1997 filing date of the provisional application (U.S.S.N. 60/047,996), from which the present application claims benefit, and since they disclose Applicants' own work, these references do not qualify as prior art to the claimed invention. This rejection may be withdrawn.

Information Disclosure Statement

Applicants also draw the Examiner's attention to the Information Disclosure Statement mailed on April 13, 2000 and request that the Form PTO-1449 submitted with that statement be initialed and returned with the next Action.

CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, such action being respectfully requested.

A marked-up version of the new claims and a clean version of all pending claims, reflecting entry of the amendments, are enclosed.

Also enclosed is a petition to extend the period for replying for two months, to and including November 6, 2001. In addition, enclosed is a Notice of Appeal, in which Applicants respectfully appeal the final rejection of the pending claims. Further enclosed is a check for the additional claim fee.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: November 6, 2001

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01997.202002 Reply to Examiner's Action Dated 6.6.01.dot

Version with Markings to Show Changes Made

Add new claims 34-64.

--34. (New) A substantially pure, naturally-occurring nucleic acid encoding a lineage-37 (LIN-37) polypeptide that is free of the genes which, in the naturally-occurring genome of the organism, flank the gene, said polypeptide having 50% or greater amino acid sequence identity to the amino acid sequence of SEQ ID NO: 1, wherein said polypeptide has the ability to alter cell proliferation.

35. (New) The nucleic acid of claim 1, wherein said nucleic acid encodes a LIN-37 polypeptide that has 85% or greater amino acid sequence identity to the amino acid sequence of SEQ ID NO:1.

36. (New) The nucleic acid of claim 1, wherein said nucleic acid encodes a LIN-37 polypeptide that has 95% or greater amino acid sequence identity to the amino acid sequence of SEQ ID NO:1.

37. (New) The nucleic acid of claim 1, wherein said nucleic acid encodes a LIN-37 polypeptide that has the ability to decrease cell proliferation.

38. (New) The nucleic acid of claim 37, wherein said nucleic acid encodes a LIN-37 polypeptide that has the ability to decrease cell proliferation by 50%.

39. (New) The nucleic acid of claim 37, wherein said nucleic acid encodes a LIN-37 polypeptide that has the ability to decrease cell proliferation by one-fold.

40. (New) A substantially pure, naturally-occurring synMuv nucleic acid comprising nucleic acid having 50% or greater nucleotide sequence identity to the nucleotide sequence of SEQ ID NO: 2, wherein said nucleic acid encodes a polypeptide having the ability to alter cell proliferation.

41. (New) The synMuv nucleic acid of claim 10, wherein said synMuv nucleic acid comprises a nucleic acid sequence that has 85% or greater nucleotide sequence identity to the nucleotide sequence of SEQ ID NO:2.

42. (New) The synMuv nucleic acid of claim 10, wherein said synMuv nucleic acid comprises a nucleic acid sequence that has 95% or greater nucleotide sequence identity to the nucleotide sequence of SEQ ID NO:2.

43. (New) The synMuv nucleic acid of claim 10, wherein said synMuv nucleic acid encodes polypeptide that has the ability to decrease cell proliferation.

44. (New) The synMuv nucleic acid of claim 43, wherein said synMuv nucleic acid encodes a polypeptide that has the ability to decrease cell proliferation by 50%.

45. (New) The synMuv nucleic acid of claim 43, wherein said synMuv nucleic acid encodes a polypeptide that has the ability to decrease cell proliferation by one-fold.

46. (New) A cell which contains a substantially pure naturally occurring nucleic acid encoding a lineage-37 (LIN-37) polypeptide that is free of the genes which, in the naturally-occurring genome of the organism, flank the gene, said polypeptide having 50% or greater amino acid sequence identity to SEQ ID NO: 1, wherein said polypeptide has the ability to alter cell proliferation.

47. (New) The cell of claim 16, wherein said nucleic acid encodes a LIN-37 polypeptide that has 85% or greater amino acid sequence identity to the amino acid sequence of SEQ ID NO:1.

48. (New) The cell of claim 16, wherein said nucleic acid encodes a LIN-37 polypeptide that has 95% or greater amino acid sequence identity to the amino acid sequence of SEQ ID NO:1.

49. (New) The cell of claim 16, wherein said nucleic acid encodes a LIN-37 polypeptide that has the ability to decrease cell proliferation.

50. (New) The cell of claim 49, wherein said nucleic acid encodes a LIN-37 polypeptide that has the ability to decrease cell proliferation by 50%.

51. (New) The cell of claim 49, wherein said nucleic acid encodes a LIN-37 polypeptide that has the ability to decrease cell proliferation by one-fold.

52. (New) A transgenic cell which contains a substantially pure naturally-occurring nucleic acid encoding a lineage-37 (LIN-37) polypeptide having 50% or greater amino acid sequence identity to SEQ ID NO: 1, wherein said polypeptide has the ability to alter cell proliferation.

53. (New) The transgenic cell of claim 18, wherein said nucleic acid encodes a LIN-37 polypeptide that has 85% or greater amino acid sequence identity to the amino acid sequence of SEQ ID NO:1.

54. (New) The transgenic cell of claim 18, wherein said nucleic acid encodes a LIN-37 polypeptide that has 95% or greater amino acid sequence identity to the amino acid sequence of SEQ ID NO:1.

55. (New) The transgenic cell of claim 18, wherein said nucleic acid encodes a LIN-37 polypeptide that has the ability to decrease cell proliferation.

56. (New) The transgenic cell of claim 55, wherein said nucleic acid encodes a LIN-37 polypeptide that has the ability to decrease cell proliferation by 50%.

57. (New) The transgenic cell of claim 55, wherein said nucleic acid encodes a LIN-37 polypeptide that has the ability to decrease cell proliferation by one-fold.

58. (New) A substantially pure, naturally-occurring *lineage-37* (*lin-37*) nucleic acid having about 50% or greater nucleotide sequence identity to SEQ ID NO: 2 isolated according to the method comprising:

(a) providing a cell sample;

(b) introducing by transformation into said cell sample a candidate *lin-37* nucleic acid;

(c) expressing said candidate *lin-37* nucleic acid within said cell sample; and

(d) determining whether said cell sample exhibits an altered cell proliferation response, whereby an altered level of cell proliferation identifies a *lin-37* nucleic acid.

59. (New) The *lin-37* nucleic acid of claim 25, wherein said *lin-37* nucleic acid has 85% or greater nucleotide sequence identity to the nucleotide sequence of SEQ ID NO: 2.

60. (New) The *lin-37* nucleic acid of claim 25, wherein said *lin-37* nucleic acid has 95% or greater nucleotide sequence identity to the nucleotide sequence of SEQ ID NO: 2.

61. (New) A substantially pure, naturally-occurring *lineage-37* (*lin-37*) nucleic acid having about 50% or greater nucleotide sequence identity to SEQ ID NO: 2 isolated according to the method comprising:

(a) providing a cell sample;

(b) introducing by transformation into said cell sample a candidate *lin-37* nucleic acid;

(c) expressing said candidate *lin-37* nucleic acid within said cell sample; and

(d) determining whether said cell sample exhibits an altered cell proliferation response, whereby a decreased level of cell proliferation identifies a *lin-37* nucleic acid.

62. (New) The *lin-37* nucleic acid of claim 25, wherein said *lin-37* nucleic acid has the ability to decrease cell proliferation.

63. (New) The *lin-37* nucleic acid of claim 62, wherein said *lin-37* nucleic acid has the ability to decrease cell proliferation by 50%.

64. (New) The *lin-37* nucleic acid of claim 62, wherein said *lin-37* nucleic acid has the ability to decrease cell proliferation by one fold.--